Exertional rhabdomyolysis following return to exercise after COVID-19 lockdown

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Rhabdomyolysis is a potentially life-threatening disorder of severe muscle injury. It results in the classical clinical syndrome of myalgia, muscle weakness and swelling, and leads to dark urine due to myoglobinuria in severe cases. Release of intracellular products creatine kinase (CK), potassium and myoglobin can result in systemic complications, including acute kidney injury, hyperkalaemia and acidosis. Causes include direct muscle trauma, ischaemia, infection, toxins, hyperthermia and acquired or genetic myopathies.1

Exertional rhabdomyolysis (ER) represents the severe end of the spectrum of exercise-induced muscle injury, which also includes delayed-onset muscle soreness (DOMS) and asymptomatic hyper-CKaemia.2 Although there is no universally agreed definition of rhabdomyolysis, the combination of clinical symptoms and peak CK>1,000U/L (or >5x upper limit of normal) is commonly used to define mild rhabdomyolysis, after excluding alternative causes.3

Risk factors for ER include male sex, low physical fitness, heat exposure, dehydration and high-intensity, prolonged exercise, especially eccentric weight-bearing exercise.3 Occasionally ER may be the presenting feature of an inherited metabolic disorder (IMD).1,2,4 Typically these disorders of fat or glycogen metabolism are associated with recurrent episodes, although rarely a single episode may be the sole presenting feature in an otherwise asymptomatic adult.5

The National Metabolic Service has detected an increase in referrals for ER since March 2020, coinciding with the SARS-CoV2 pandemic. Lockdowns are an important public health response to COVID-19 and are associated with a decrease in physical activity.6,7 Therefore, we conducted a retrospective review of these cases to delineate the risk factors for ER with return to exercise following lockdowns.

Methods
The database of the National Metabolic Service of New Zealand was reviewed for referrals for ER since March 2020. Clinical data, and biochemical and genetic testing results (where performed), were reviewed. ER was defined by the combination of myalgia and significant hyper-CKaemia (peak CK>1,000U/L) following exercise, with or without myoglobinuria. Individuals previously investigated for ER were excluded.

Results
Nine individuals were identified. However, two were excluded, due to investigation for recurrent rhabdomyolysis prior to March 2020 or peak CK<1,000U/L. Seven individuals (age 14–38 years, six males) developed ER after a period of relative inactivity during lockdown. ER occurred after unaccustomed high-intensity weight-bearing exercise in six (upper-limb in five) and following strenuous hiking in one. All were previously active, including five who attended the gym at least three times per week prior to lockdown, and three were competitive athletes. Two cases maintained regular aerobic exercise throughout lockdown, but then developed ER after their first session of high-intensity weight-bearing exercise at the gym.

Two patients had a history suggestive of previous exertional muscle injury. Of these, one individual had several documented episodes of asymptomatic elevation of transaminases following exercise. The other had a history suggestive of a fatty acid oxidation disorder (FAOD), including recurrent hypo-
glycaemia and liver dysfunction during early childhood infections, exertional myalgia and one previous documented episode of ER. The acylcarnitine profile demonstrated elevations of very long chain fatty acyl-carnitines (C14, C14:1 and C16), and molecular genetic testing confirmed the diagnosis of very long chain acyl-CoA dehydrogenase deficiency (VLCADD). No other individuals had a history suggestive of an IMD, and acylcarnitine profiles, where performed, were normal.

Genetic testing was offered to all individuals, but four declined. Single-gene sequencing of ACADVL confirmed the diagnosis of VLCADD in one individual. Next-generation sequencing (NGS) with a rhabdomyolysis/myopathy gene panel was requested in two others, and was non-diagnostic.

All patients were admitted to hospital and treated with intravenous fluids, with good outcome. Peak CK was >10,000U/L in five cases (range 1,760–10,3000). Four had evidence of myoglobinuria, and two developed acute kidney injury, with peak creatinine 123-208 µmol/L. Three patients had at least one subsequent episode of ER. This included the individual with VLCADD, and two others who developed ER after return to exercise following subsequent lockdowns.

**Discussion**

ER following unaccustomed exercise is well described in large cohorts of students and military recruits, and is associated with intensive prescribed exercise, especially in individuals with poor fitness. In this case series, it was noteworthy that most of the affected individuals were fit and competitive athletes and developed ER after an uncharacteristic period of detraining during lockdown. Detraining is associated with a decrease in mitochondrial ATP production rate in muscle within just two weeks, and therefore ER following return to intensive exercise likely represents acute intra-cellular energy deficiency causing muscle injury. Individuals with the highest activity pre-lockdown have the largest decrease in exercise habits, and therefore they may be more susceptible to the metabolic effects of detraining. Additionally, elite athletes may have higher capacity to persevere through strenuous novel exercise regimens, even in the setting of significant deconditioning.

Although post-lockdown ER most likely represents physiologic adaptation to acute detraining, underlying genetic muscle disorders should also be considered in the differential diagnosis. IMDs commonly presenting with recurrent ER include glycogen storage disorders (GSD), including McArdle's disease (GSD V), FAODs including VLCADD and carnitine palmitoyltransferase deficiency type II, and mitochondrial myopathies. Other genetic disorders associated with recurrent ER include RYR1 and LPIN1 disorders. The diagnostic yield of NGS panels in the setting of recurrent rhabdomyolysis is reported as 33%, but appropriate clinical and biochemical evaluation allows more targeted diagnostic testing. In this series, VLCADD was confirmed in one individual with classical FAOD symptoms, allowing prompt initiation of appropriate treatment, surveillance for complications and genetic counselling.

In conclusion, as thousands of New Zealanders return to high-intensity exercise after the longest lockdown to date, clinicians should be alert to the presentation of ER, in previously active individuals, following a prolonged period of relative inactivity. Maintenance of exercise during lockdown should be encouraged, and novel high-intensity exercise should be introduced gradually to avoid this complication. IMDs should be considered in the differential diagnosis of ER, especially in the presence of recurrent episodes, hypoglycaemia, encephalopathy, cardiomyopathy or liver disease. Discussion with the National Metabolic Service should be considered, to facilitate appropriate investigation and timely treatment.
Competing interests:
Nil.

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